

D-dimer levels for Risk Stratification in Patients with Suspected COVID-19 – A Prospective Observational Study

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Abstract

Background: Elevated D-dimer levels have been observed in COVID-19 and are of prognostic value, but have not been compared to an appropriate control group.

Methods: Observational cohort study including emergency patients with suspected or confirmed COVID-19. Logistic regression defined the association of D-dimer levels, COVID-19 positivity, age, and gender with 30-day-mortality.

Results: 953 consecutive patients (median age 58, 43% women) presented with suspected COVID-19: 12 (7.4%) patients with confirmed SARS-CoV-2-infection died, compared with 28 (3.5%) patients without SARS-CoV-2-infection. Overall, most (56%) patients had elevated D-dimer levels ($\geq 0.5\text{mg/l}$). Age (OR 1.07, CI 1.05–1.10), D-dimer levels $\geq 0.5\text{mg/l}$ (OR 2.44, CI 0.98–7.39), and COVID-19 (OR 2.79, CI 1.28–5.80) were associated with 30-day-mortality.

Conclusion: D-dimer levels are effective prognosticators in both patient groups.

Keywords

COVID-19, D-dimer levels, risk-stratification, NEWS, prognosis

Key Points

1. Many patients with suspected COVID-19 have elevated D-dimer levels, whether or not they have confirmed SARS-CoV-2 infection.
2. D-dimer levels do not differ between patients with confirmed COVID-19 and patients suspected of COVID-19 but tested SARS-CoV-2 negative.
3. D-dimer levels alone or in combination with NEWS are effective prognosticators in both patient groups.

Introduction

Several attempts have been made to develop specific risk stratification tools for COVID-19 patients^{1,2}, which might enhance traditional triage systems such as the Emergency Severity Index (ESI)³. Since abnormal coagulation has been observed in COVID-19^{4,5} and D-dimer levels are a predictor of short-term survival in undifferentiated patients^{6–10}, adding D-dimer measurement to the clinical assessment of COVID-19 patients may be of benefit. Although D-dimer levels are higher in COVID-19 patients with poor outcomes^{11–13}, it is not known how D-dimer levels in COVID-19 patients compare to levels in patients with other equally severe infections.¹⁴

Unlike other studies, this study compared D-dimer levels in patients with confirmed SARS-CoV-2 infection with those of patients who on

presentation were suspected of having SARS-CoV-2 infection but subsequently showed no evidence of it. Mortality by 30 days after presentation and ICU admission within 30 days were used as outcomes.

Furthermore, since several other studies suggest that NEWS¹⁵ and D-dimer are useful for risk-stratification^{16–19} and outcome prediction of patients with and without COVID-19^{20–23}, this study additionally examined the possible value of using both these variables to risk-stratify patients attending our Emergency Department (ED) with suspected COVID-19.

Methods

Study design and setting

We conducted a prospective, observational, cohort COReNAVirus surviVAL (COVIVA, ClinicalTrials.

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D-dimer levels for Risk Stratification in Patients with Suspected COVID-19 – A Prospective Observational Study

gov NCT04366765) study including unselected adult patients attending the ED of the University Hospital of Basel, a tertiary care center with approximately 54,000 annual ED visits. During the first wave of the pandemic, we established a Triage and Test Center (TTC) in a nearby church where all patients with suspected COVID-19 were tested for the presence of SARS-CoV-2.²⁴ All patients were screened by a senior physician for main symptoms and acuity on arrival at the TTC as described elsewhere.²⁴ The Physicians' Disease Severity Rating (PDSR) was used as an informal triage tool to identify patients in need of further clinical evaluation. PDSR has been shown to be non-inferior to formal triage tools regarding adverse outcomes and has also been shown to be safe in our TTC.^{24,25} In patients assigned a PDSR > 2 the NEWS was measured and patients were evaluated further by another senior physician. Patients who had a NEWS > 2, oxygen saturation < 94% or who were deemed to be ill, were referred to our ED for further work-up.²⁴ All other patients were directly sent into home quarantine after the SARS-CoV-2 swab was performed. Besides referrals from the TTC, self-presentations and referrals by ambulance to our ED were eligible for the study if they met the study inclusion criteria.

Population and inclusion criteria

All patients aged 18 years and older presenting with suspected SARS-CoV-2 infection to the ED of the University Hospital in Basel, Switzerland, during the first wave of COVID-19 pandemic between March 2020 and June 2020 were eligible for inclusion in the study. SARS-CoV-2 infection was suspected in any patient with breathlessness, other respiratory symptoms or flu-like symptoms such as fever, chills, sore throat, cough, myalgia, headache.²⁴ In addition, patients with acute confusion or general deterioration were considered, if these symptoms could not be explained otherwise. At the beginning, patients were not asked if they had hyposmia/anosmia or hypogeusia/ageusia, because at the time of this study these symptoms had not been identified as predictors of SARS-CoV-2 infection.

Patients with suspected COVID-19 were evaluated in a dedicated respiratory sector in the ED. All patients underwent nasopharyngeal SARS-CoV-2 swab tests. Patients were considered COVID-19 positive cases if one or multiple SARS-CoV-2 PCR swab tests performed at day of ED presentation or within 14 days prior to or post ED presentation was COVID-19 positive, whereas patients with consistently negative SARS-CoV-2 swab test results were considered COVID-19 negative (serving as controls).

Data collection

All patients underwent a comprehensive clinical assessment by the treating ED physician according to local standard operating procedure. Where possible, vital signs including body temperature, heart rate, blood pressure, oxygen saturation and breathing rate were documented in every patient. The patients' management, including disposition decisions, was left to the discretion of the attending physicians and was done in accordance with local standard operating procedures.

At ED presentation blood samples were immediately drawn in every patient (both case and control). Routine laboratory parameters, including D-dimer were determined in every patient as part of the local standard operating procedure in patients suspected to have COVID-19. Timing and type of subsequent laboratory measurements during hospital stay were left to the discretion of the treating physicians and were not analyzed.

D-dimer levels: D-dimer levels at ED presentation were measured using the fully automated latex immunoassay ACL TOP 750 (Werfen GmbH, Instrumentation Laboratory, Germany, de.werfen.com) with a quantification range of 0.3mg/l to 20mg/l. D-dimer levels below 0.3mg/l were counted as 0.29mg/l and values >20mg/l were counted as 20.01mg/l for data analysis.

Follow-Up:

Thirty days after discharge, patients were contacted by telephone calls or in written form by research physicians or study nurses, guided by a predefined set of questions and item-checklists. Records of hospitals and primary care physicians, as well as national death registries, were screened for additional information, if applicable.

Ethics

All participating patients or their legally authorized representatives consented by signing a local general consent form. This study was conducted according to the principles of the Declaration of Helsinki, approved by the local ethics committee (EKNZ identifier 2020-00566). The authors designed the studies, gathered, analyzed and present the data according to the STROBE guidelines.²⁶

Outcome measures and statistical analysis

Primary outcome was 30-day-all-cause-mortality, defined as death within 30 days after ED presentation. Secondary outcomes were ICU admissions within 30 days and a composite outcome consisting of the combination of 30-day mortality and ICU admission.

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D-dimer levels for Risk Stratification in Patients with Suspected COVID-19 – A Prospective Observational Study

Descriptive statistics are presented as counts and percentages for categorical data and median with interquartile range for metric variables. Comparisons between groups were done using Kruskal-Wallis test (for median) and chi-squared test, or exact Fisher tests in cells with expected frequencies below $n=5$. D-dimers were log10 transformed to achieve approximate normal distribution. Logistic regression was performed for both primary and secondary outcomes, adjusted for age and gender. The results are shown as Odds Ratio (OR), 95% confidence interval (CI) and p-values (P). Unadjusted ORs were calculated using chi-squared test from count data, where appropriate. For models with zero counts in the cross-table, a Bayesian generalized linear model approach was performed, with a weakly informative prior as described by Gelman et al.²⁷ This was chosen because a zero count in a cross-table results in an undefined OR. Primary outcome is graphically presented in a cox regression survival curve with combined strata for COVID-19 status and D-dimer levels, adjusted for age and gender. Cox regression was only used for the graphical description, but not

for the calculation of p-values between sub-groups. In one sub-group no event was counted. Therefore, hazard ratios cannot be estimated accurately, hence Bayesian logistic regression was performed as described above.

For patients who re-presented to the ED only the index visit was counted, and subsequent presentations were excluded from the analysis. A p-value significance was set at <0.05 . The entire analysis was performed using the statistical software R version 4.0.3. (<https://www.r-project.org/>)

Results

Baseline characteristics

Out of 1086 ED presentations suspected to be COVID-19 infections during the study period, 133 were excluded; 50 because they were re-presentations, 78 because D-dimer levels were not measured, and 5 were lost to follow-up. This yielded a population for the study of D-dimer levels of 953 patients (Figure 1).

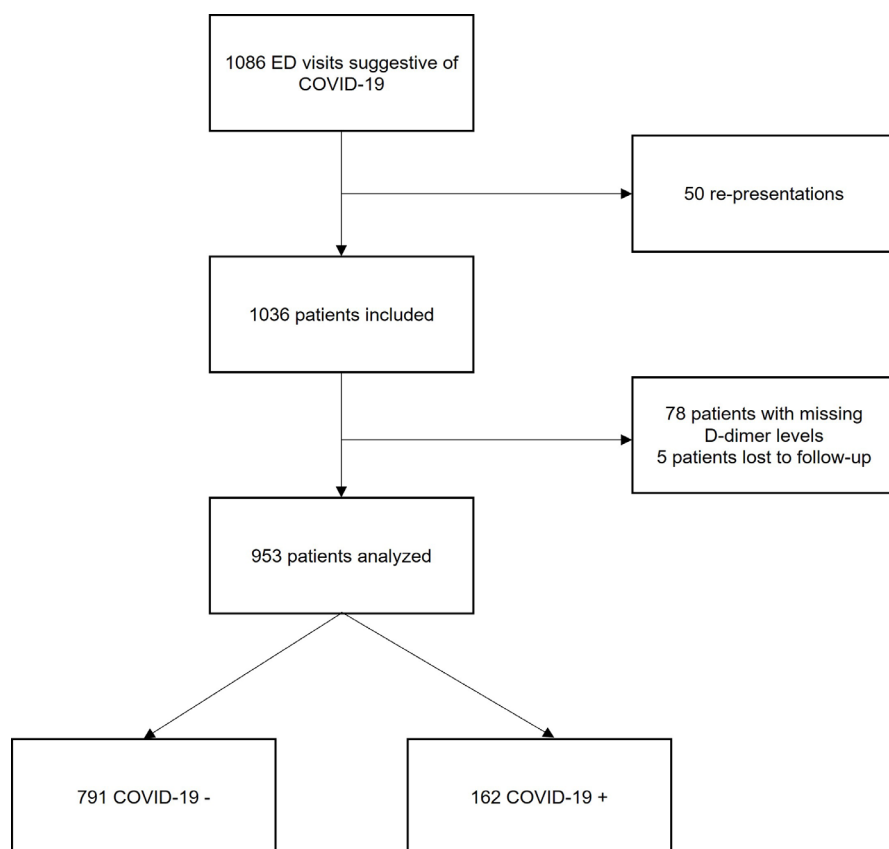


Figure 1: Flow of patient inclusion process

Exclusion of 50 re-presentations and 78 with missing D-dimer levels on ED presentation. Additional 5 patients were lost to 30-day follow-up. Final study population N = 953.

D-dimer levels for Risk Stratification in Patients with Suspected COVID-19 – A Prospective Observational Study

The majority of the study patients (750, 78.7%) were referred to the ED via the TTC and 59 (6.2%) patients were direct self-referrals to the ED. Additional 144 (15.1%) patients were transported by ambulance.

The population of 953 patients had a median age of 58 (IQR 42–74), ranging from 18 to 100 years; 411 (43%) were female. Most patients were COVID-19 negative (791, 83%) and 162 (17%) patients tested COVID-19 positive. Compared to COVID-19 negative patients, those who were COVID-19 positive were more likely assigned an ESI level 1, more likely to be admitted to ICU from the ED, and to die within 30 days after ED presentation. In those assessed, COVID-19 positive patients had higher NEWS points ($P = 0.047$), a higher respiratory rate ($P = 0.018$) and increased body temperatures ($P = 0.005$). However, there were no differences in age ($P = 0.529$), gender distribution ($P = 0.646$), D-dimer levels ($P = 0.183$), heart rate ($P = 0.314$), systolic blood pressure ($P = 0.067$) or oxygen saturation ($P = 0.058$) (see Table 1).

D-dimer levels

Overall, more than half of all patients (536, 56.2%) had an elevated D-dimer level (≥ 0.5 mg/l). The median D-dimer level did not differ significantly between COVID-19 negative and COVID-19 positive patients (median 0.59, IQR [0.29, 1.21] vs. 0.60, IQR [0.35, 1.22]; $P = 0.183$) (for visualization see Figure 2). Age and D-dimer levels were positively correlated, independent of COVID-19 status ($P < 0.001$) (see Figure 3).

Primary outcome: 30-day-mortality rate

Overall, 40 (4.2%) of 953 patients died within 30 days; 28 (3.5%) of the patients tested COVID-19 negative, and 12 (7.4%) of the patients tested COVID-19 positive. Five of these patients were transferred to ICU before a complete set of vital signs could be documented in the study file; all of them had a D-dimer ≥ 0.5 mg/l and three were COVID-19 positive patients.

Patients with a D-Dimer ≥ 0.5 mg/l were more likely to die (unadjusted OR 5.76, CI 2.24–14.83, $P < 0.001$). Of the patients with a D-dimer ≥ 0.5 mg/l, more COVID-19 positive than COVID-19 negative patients died (unadjusted OR 2.67, CI 1.28–5.57, $P = 0.01$). In contrast, of the patients with a D-dimer < 0.5 mg/l, none of the 68 COVID-19 positive patients and 5 of the 349 (1.4%) COVID-19 negative patients died; this difference was not statistically significant (unadjusted OR 0.27 CI 0.01–5.30 $P = 0.39$). The worst outcome was observed in patients who tested COVID-19 positive with elevated D-dimer levels

(≥ 0.5 mg/l) (see Figure 4). In univariate analysis, age, SARS-CoV-2 infection and D-dimer ≥ 0.5 mg/l, but not gender, were associated with 30-day mortality. In multivariate analysis, including age, gender, D-dimer ≥ 0.5 mg/l and SARS-CoV-2-infection, age and SARS-CoV-2 infection retained their significance, whereas D-dimer levels did not (Table 2).

Secondary outcomes

Altogether, 76 of 953 (8%) patients were admitted to the ICU within 30 days after ED admission, 45 (5.7%) COVID-19 negative and 31 (19.1%) COVID-positive patients. The composite outcome was observed in 104 (10.9%) patients; 70 (8.8%) were COVID-19 negative and 34 (21%) were COVID-19 positive. Patients with an elevated D-dimer level (≥ 0.5 mg/l) were more likely to be admitted to the ICU (adjusted OR 2.47, CI 1.38–4.61, $P = 0.003$) and more likely to reach the composite outcome (adjusted OR 2.24, CI 1.34–3.86, $P = 0.003$) (Table 2). Both, D-dimer levels, and COVID-19 status were predictive for ICU admission or the composite outcome within 30 days. Age was predictive for the composite outcome, but not for ICU admission (Table 2).

Risk stratification with D-dimer levels and NEWS combined

In 52 (5.5%) patients, a complete set of vital signs were not recorded at ED presentation so that NEWS could not be calculated. Therefore, D-dimer levels and NEWS could only be studied in 901 patients (see Table 1 and Figure 5). In this subgroup of the 901 patients with D-dimer levels and a complete set of vital signs, COVID-19 positive patients were no more likely to die than COVID-19 negative patients: 8 of 147 (5.4%) COVID-19 positive patients died compared with 27 of 727 (3.6%) COVID-19 negative patients (unadjusted OR 1.55, CI 0.69–3.48, $P = 0.29$). For patients who had a NEWS ≥ 3 and a D-dimer level ≥ 0.5 mg/l, 8 of 48 (16.6%) COVID-19 positive patients died, compared with 17 of the 234 (7.3%) COVID-19 negative patients (unadjusted OR 2.55, CI 1.03–6.31, $P = 0.04$). Although not statistically significant, of the patients with a NEWS < 3 , none of the 69 COVID-19 positive patients died, compared with 7 of the 436 (1.6%) COVID-19 negative patients (unadjusted OR 0.25 CI 0.01–4.64, $P = 0.35$) (Figure 5). Five patients with a D-dimer level below 0.5 mg/l died: three patients had a NEWS ≥ 3 and of the two patients with a NEWS < 3 , one was 94 years old and frail (as documented by a Clinical Frailty Scale of 6), and the other one died of a suspected drug overdose. (Figure 5).

D-dimer levels for Risk Stratification in Patients with Suspected COVID-19 – A Prospective Observational Study

Table 1. Baseline characteristics of patients stratified by COVID-19 result

	N available observations	All patients	COVID-19 negative	COVID-19 positive	P
N		953 (100)	791 (83)	162 (17)	
Age (years)	953	58 [42, 74]	59 [41, 74]	57 [44, 69]	0.529
Female gender	953	411 (43.1)	338 (42.7)	73 (45.1)	0.646
30-day mortality	953	40 (4.2)	28 (3.5)	12 (7.4)	0.043
Occurrence of PE¹	953	28 (2.9)	23 (2.9)	5 (3.1)	0.802
D-dimer level (mg/l)	953	0.59 [0.29, 1.21]	0.59 [0.29, 1.21]	0.60 [0.35, 1.22]	0.183
D-dimer ≥ 0.5 mg/l	953	536 (56.2)	442 (55.9)	94 (58.0)	0.678
ESI	953				<0.001
1		18 (1.9)	10 (1.3)	8 (5.2)	
2		360 (38.6)	318 (40.8)	42 (27.3)	
3		489 (52.4)	391 (50.2)	98 (63.6)	
4		65 (7.0)	59 (7.6)	6 (3.9)	
5		1 (0.1)	1 (0.1)	0 (0.0)	
NEWS	901	2 [1, 4]	2 [1, 4]	3 [1, 5]	0.047
Heart rate (bpm)	918	88 [76, 103]	88 [75, 103]	89 [80, 102]	0.314
Systolic BP² (mmHg)	899	137 [122, 155]	138 [122, 156]	134 [122, 149]	0.067
Respiratory rate (bpm)	908	19 [16, 23]	18 [16, 22]	20 [16, 24]	0.018
Body temperature (°C)	913	37 [36.5, 37.7]	37 [36.5, 37.7]	37.1 [36.8, 38.0]	0.005
Oxygen saturation (%)	922	97 [95, 98]	97 [95, 98]	97 [95, 98]	0.058
Initial disposition	953				<0.001
Outpatient		481 (50.5)	414 (52.3)	67 (41.4)	
Medical ward		412 (43.2)	338 (42.7)	74 (45.7)	
ICU		60 (6.3)	39 (4.9)	21 (13.0)	

The table comprises baseline characteristics of all patients included in the study (N=953). Results are presented as median [IQR] or count (%). For each variable, the number of patients with available data is presented in the first column. ¹Occurrence of PE = Pulmonary embolism within 30 days after ED presentation. ²BP = Blood pressure.

Discussion

In this observational study, no difference in median D-dimer levels between patients with and without confirmed SARS-CoV-2 infection was found. More than half of all patients suspected of SARS-CoV-2 infection (of whom only 17 % were positive) had elevated D-dimer levels. Age, a D-dimer level ≥ 0.5 , a NEWS ≥ 3 and COVID-19 positivity all predicted 30-day mortality, and all but age predicted admission to ICU.

After infection with SARS-CoV-2, approximately 20% of patients deteriorate within 7 days and present with hypoxia that may require intensive care for respiratory support.^{13,28} Therefore, an accurate predictive tool for the likely course of the illness is needed, and several have been proposed.^{1,29–32} During the current pandemic, more than a third of Danish hospitals have implemented routine measurement of D-dimer levels for prognostication on all patients with suspected COVID-19.³³ There is a wide spectrum of causes to

D-dimer levels for Risk Stratification in Patients with Suspected COVID-19 – A Prospective Observational Study

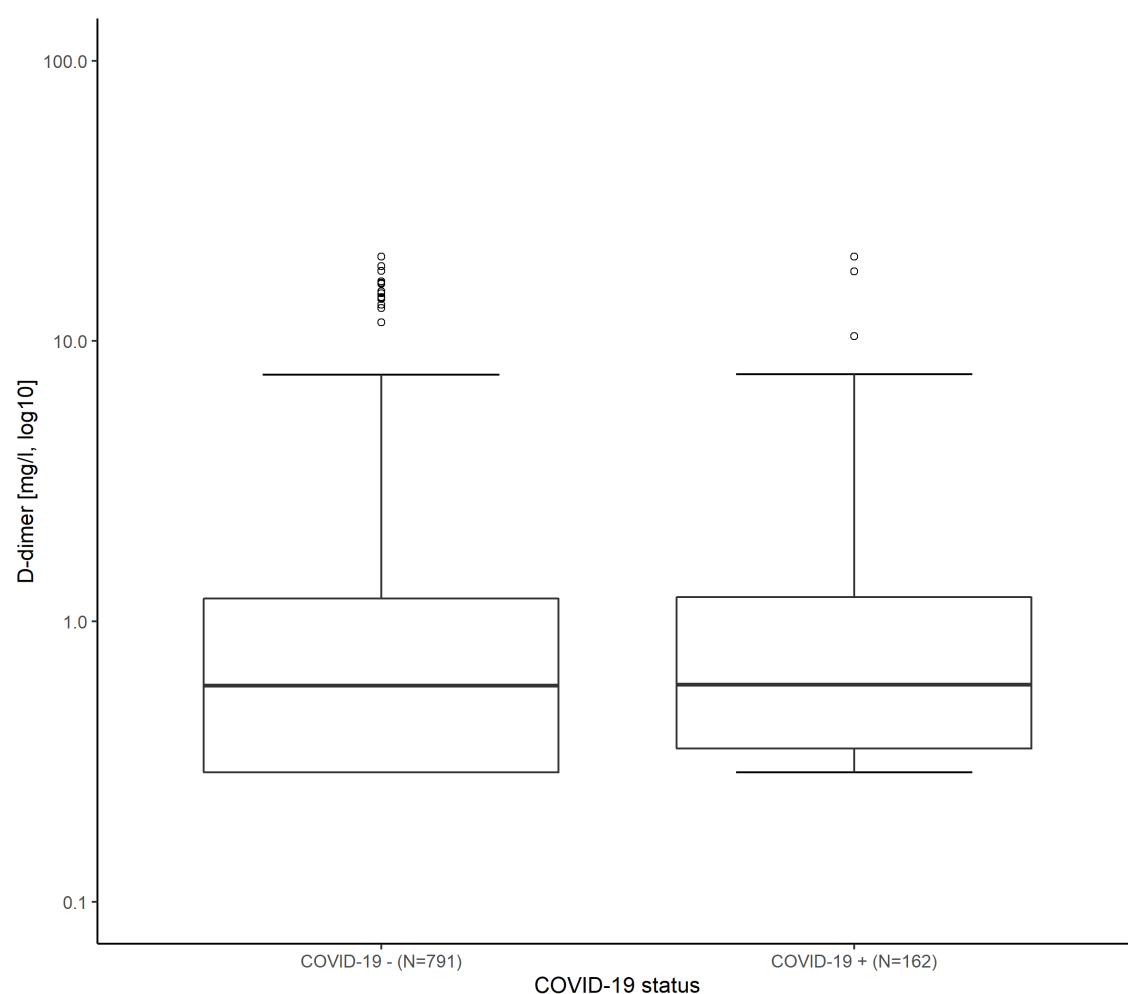


Figure 2: D-dimer levels in COVID-19 negative and COVID-19 positive patients

Figure 2 D-dimer levels at time of ED presentation (N=953) in COVID-19 negative and COVID-19 positive patients. Median is represented as a horizontal line inside the box, interquartile ranges are represented by the box's borders. D-Dimer values were log10 transformed to fit all values on the plot.

Table 2. Adjusted Odds Ratios for primary and secondary outcomes

	30-Day-Mortality (n = 40)			ICU-Admission (n = 76)			Composite Outcome (n = 104)		
	AOR	CI	P	AOR	CI	P	AOR	CI	P
Age, y	1.072	1.045-1.103	<0.001	1.012	0.998-1.027	0.095	1.027	1.014-1.041	<0.001
Female gender	0.858	0.429-1.676	0.658	0.828	0.501-1.350	0.453	0.870	0.563-1.334	0.527
D-dimer ≥ 0.5	2.438	0.982-7.392	0.077	2.465	1.378-4.606	0.003	2.236	1.340-3.857	0.003
Covid-19 +	2.788	1.284-5.795	0.007	4.093	2.457-6.762	<0.001	3.005	1.865-4.787	<0.001

The table comprises results of a logistic regression model for primary and secondary outcomes (n=953), including 4 independent variables: age, gender, D-dimer level ≥ 0.5 , COVID-19. All Odds Ratios are adjusted for the variables included in the table. AOR = Adjusted Odds Ratio, CI = 95%-Confidence Interval, P = p-value

D-dimer levels for Risk Stratification in Patients with Suspected COVID-19 – A Prospective Observational Study

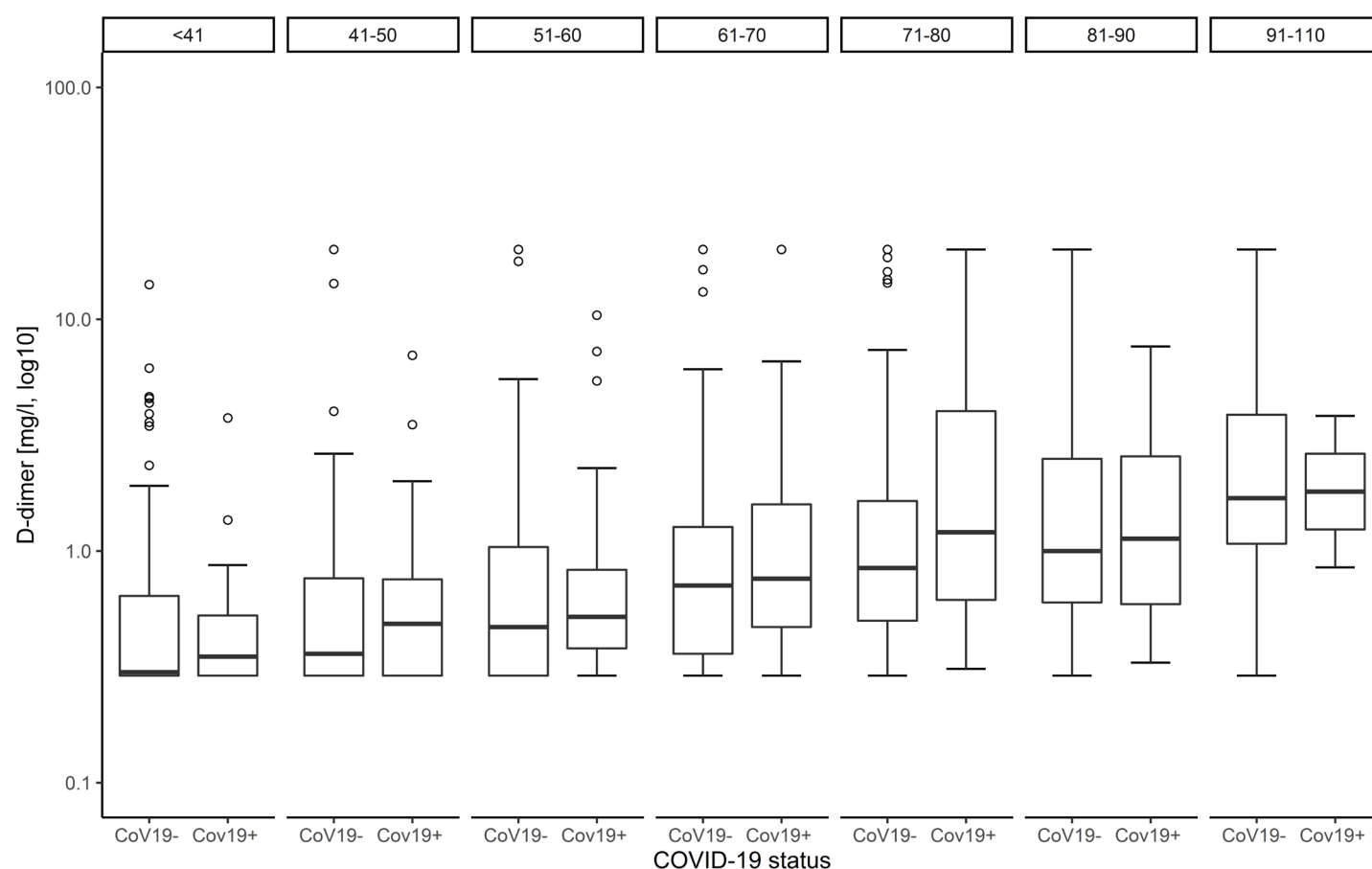


Figure 3: D-dimer level in COVID-19 negative and COVID-19 positive patients over age decade groups

D-dimer levels are compared between patients with and without COVID-19, categorized in age decade groups: <41 (n=219), 41-50 (n=122), 51-60 (n=155), 61-70 (n=158), 71-80 (n=160), 81-90 (n=118), 91-110 (n=21). Median is represented as a horizontal line inside the box, interquartile ranges are represented by the box's borders D-Dimer values were log10 transformed to fit all values on the plot.

elevated D-dimer levels,^{14,34} yet D-dimer elevation regardless of the cause, appears to be relevant for the patient's outcome.^{6,18,35} More than half of all patients in the present study had elevated D-dimer levels, which is in line with a previous study.¹⁴ D-dimer levels increase with age, as shown previously in a general population, as well as in patients with pulmonary embolism.^{34,36,37} This present study shows that the age-dependent increase in D-dimer level is independent of COVID-19 status. There seems to be an interplay between inflammation and thrombosis, and the thrombogenic activity of COVID-19 has been suggested to be higher than in other disease entities.^{5,38-40} However, concurrent pulmonary embolism occurs in 5.9% of patients hospitalized with chronic obstructive pulmonary disease (COPD) and acutely worsening respiratory symptoms⁴¹ and in 16.1% of unexplained COPD

exacerbations,⁴² compared to 3% in patients with suspected COVID-19 in our study.

Lastly, D-dimer levels and NEWS combined were explored. Very few patients in our study died with a low NEWS (<3) and low D-dimer levels (<0.5mg/l) at ED presentation. This finding is similar to previous studies suggesting that low NEWS and low D-dimer identifies patients at low risk of death.^{16,17} Rapid deterioration of vital signs might be a key point in the difference between COVID-19 and other respiratory infections,⁴³ which emphasizes the importance of monitoring vital signs in these patients. Although the use of NEWS to detect rapid deterioration in COVID-19 patients has been questioned,⁴³ other studies indicate the efficacy of NEWS is unchanged in COVID-19 patients.^{44,45} This study also found that a combination of D-dimer levels and NEWS was equally effective at identifying

D-dimer levels for Risk Stratification in Patients with Suspected COVID-19 – A Prospective Observational Study

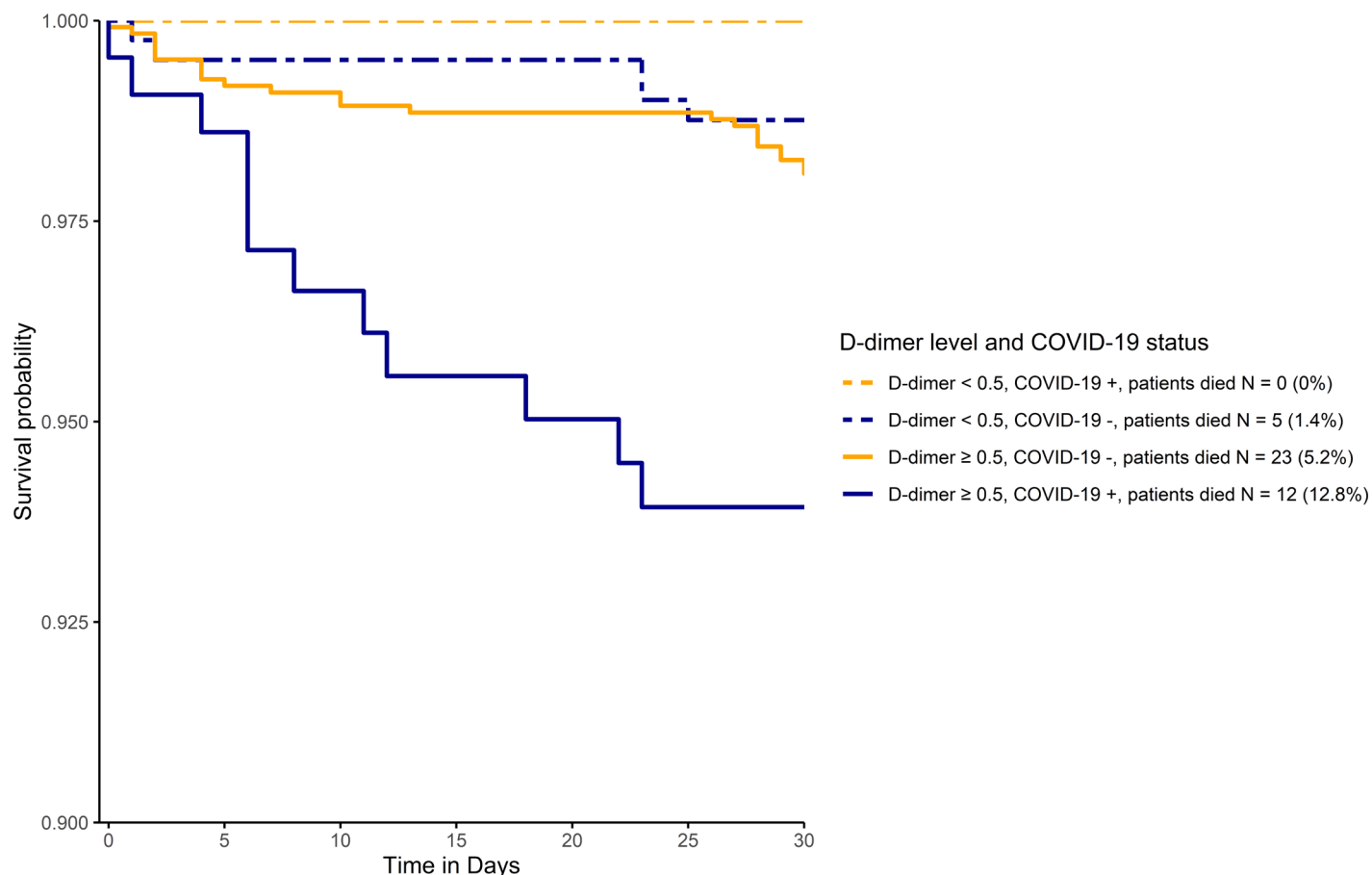


Figure 4: Graphical description of cox regression predicting 30-day survival adjusted for age and gender

Graphical description based on Cox regression with endpoint of 30-day survival, combining COVID-19 status and D-dimer level ($\geq 0.5\text{mg/l}$, $< 0.5\text{mg/l}$) as strata, adjusted for age and gender from 953 patients. The plot was cropped to 0.9–1.0 on the y-axis to improve readability. Bayesian logistic regression has shown a significant difference between patients with high D-dimer level and COVID-19 negative status (yellow solid line), and the reference group with high D-dimer level and a COVID-19 positive status (blue solid line) ($P = 0.004$).

low and high risk patients with and without SARS-CoV-2 infection.

Limitations: This is a single-center study, limiting external validity. We excluded patients with missing D-dimer levels at ED presentation, who were generally those with a worse outcome, as D-dimer levels are mainly used as a screening parameter in our ED (as in other settings³³). Only D-dimer levels at time of ED presentation were analyzed and no dynamic assessment occurred. Thus, no statement about its use or variability regarding the subsequent course of the disease after 30 days can be made. The study of the combined use of D-dimer level and NEWS was affected by 52 patients with incomplete sets of vital signs, in which NEWS could not be calculated. Additionally, changes in vital signs were not monitored. Data completeness was especially

challenging in high-urgency patients⁴⁶ and is in line with the amount of missing data in previous studies.⁴⁶ (see Figure 5, legend).

Conclusion

This prospective study found most patients with suspected COVID-19 had elevated D-dimer levels. D-dimer levels were comparable in patients with and without confirmed infection. D-dimer levels alone or in combination with NEWS are associated with 30-day mortality in both patient groups.

Declaration of Competing Interest

RT reports research support from the Swiss National Science Foundation (Grant No P300PB_167803), the Swiss Heart Foundation, the Swiss Society of Cardiology, the Cardiovascular Research Foundation

D-dimer levels for Risk Stratification in Patients with Suspected COVID-19 – A Prospective Observational Study

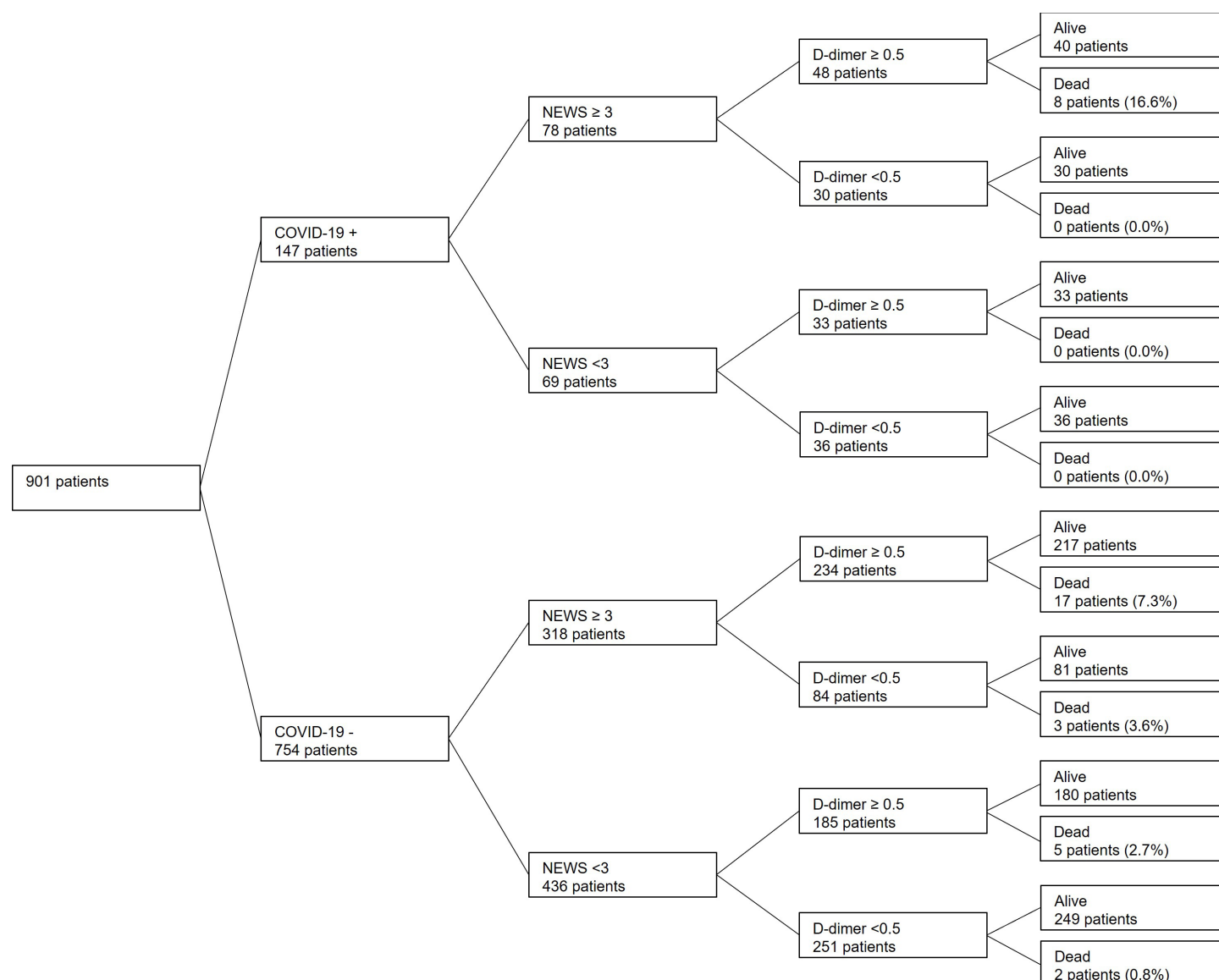


Figure 5: Flow chart of 30-day mortality according to D-dimer level and NEWS

Flow chart of 30-day mortality in 901 patients according to COVID-19 status, D-dimer (<0.5, ≥0.5mg/l) and NEWScore (<3, ≥3). In 52 patients, NEWS was not documented and could therefore not be studied.

Of note: There were more ESI 1 (6 of 52 (12.2%) versus 12 of 901 (1.4%) ESI 1) and more ESI 2 (25 of 52 (51%) versus 335 of 901 (38%)) in patients with incomplete vital signs in comparison to patients with complete measurements. Additionally, a higher proportion of patients with missing NEWS were admitted to the hospital, including medical ward and Intensive Care Unit (39 of 52 (75%) versus 433 of 901 (48%), respectively).

Basel, the University of Basel and the University Hospital Basel and a Research Grant from Roche Diagnostics; JK is founder and major shareholder of Tapa Healthcare DAC, a start-up medical software company. The other authors have nothing to declare.

Funding

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Ethics

This study was conducted according to the principles of the Declaration of Helsinki, approved by the local ethics committee (EKNZ identifier 2020-00566).

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D-dimer levels for Risk Stratification in Patients with Suspected COVID-19 – A Prospective Observational Study

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D-dimer levels for Risk Stratification in Patients with Suspected COVID-19 – A Prospective Observational Study

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